Best of the 2012 AUA Annual Meeting

Highlights From the 2012 American Urological Association Meeting, May 19-23, 2012, Atlanta, GA

[Rev Urol. *2012;14(3/4):90-103 doi: 10.3909/riu0563*]

KEY WORDS

Chronic pelvic pain syndrome • Chronic prostatitis • Prostate cancer • Radical prostatectomy • Stress urinary incontinence • Autologous muscle-derived cells • Kidney stones

Over 2300 posters, abstracts, and videos were presented at the annual meeting of the American Urological Association (AUA), held this year in Atlanta, Georgia, May 19-23, 2012. The editors of *Reviews in Urology* have culled an enormous volume of information from this premier source and present those findings that are the most relevant to the practicing urologist.

Reviewed by J. Curtis Nickel MD, FRCSC, Queen's University, Kingston, Ontario, Canada; Alan W. Partin, MD, PhD, The James Buchanan Brady Urological Institute, The Johns Hopkins Medical Institutions, Baltimore, MD; Jayabalan Nirmal, PhD, Michael B. Chancellor, MD, William Beaumont Hospital, Royal Oak, MI; Stacy Loeb, MD, New York University, New York, NY; Michael K. Brawer, MD, URIDEA, Seattle, WA; Dean Assimos, MD, Wake Forest University School of Medicine, Winston-Salem, NC; Ellen Shapiro, MD, FACS, FAAP, New York University School of Medicine, New York, NY.

Optimizing Care for Urological Chronic Pelvic Pain Syndromes

A plenary session panel presented on the last morning of the AUA Annual Meeting included a discussion with four clinician/researchers in the field of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and interstitial cystitis/bladder pain syndrome (IC/BPS) on how to incorporate the latest research findings in the field into practical urologic practice.[1] The clear message was that, although there is, as yet, no cure for urologic CPPS (UCPPS), urologists can help to ameliorate the pain and improve the quality of life for patients using the treatments we currently have available.

As the chairperson of the session, Dr. J. Curtis Nickel (Queen's University, Kingston, Ontario, Canada) stated that these conditions are very prevalent (2% to 4% of men and women), represent a significant proportion of urological outpatient practice (> 5%), and yet remain the most enigmatic and frustrating conditions that urologists have to

deal with in daily clinical practice. The patients' quality of life is dismal, mirroring that of other major chronic medical conditions such as active Crohn's disease, insulin-dependent diabetes, and congestive heart failure. Because it affects patients of all ages, the condition results in an enormous expense in terms of direct and indirect costs to both society and individual patients. The diagnosis is one of exclusion (which surgeons do not like) and the treatment regimens and strategies, to date, have been rather dismal. There are only two US Food and Drug Administration (FDA)–indicated interventions for BPS (oral pentosanpolysulfate sodium and intravesical dimethyl sulfoxide [DMSO]). At best, they provide only modest benefit in a small percentage of patients. And for men with CPPS, there are no FDA-indicated medical or other interventions. So, not only does this condition represent the greatest unmet need in urology, it also represents the greatest opportunity for advances.

During the panel discussion, the speakers outlined how these conditions should be evaluated. Their recommendations are described in Table 1 and Table 2.

Dr. Nickel presented the evidence from available randomized, placebo-controlled clinical trials for CP/CPPS therapy using a unique network meta-analytical approach and indicated that, although our standard medical therapies provide statistically significant treatment effects, they are, at most, barely clinically significant and, furthermore, there is a disconnect between overall benefit in the entire population and individual responses (Table 3). Therefore, traditional therapies can remain as part of our CP/CPPS treatment strategy, but monotherapy is not really effective.

The UPOINT phenotype system was introduced as a clinical tool, using our standard urologic evaluation, to differentiate patients into one or more of six distinct phenotypic domains (Table 4). The traditional therapies are then directed, in a multimodal fashion, toward the different phenotypes identified in each individual patient. Dr. Nickel reported that this approach will lead to clinically

TABLE 1

Evaluation of a Man With Chronic Prostatitis/Chronic Pelvic Pain Syndrome

- History
- Validated symptom score (eg, the chronic prostatitis symptom index)
- Physical examination, including digital rectal and pelvic floor assessment
- Investigations
  - Urinalysis, lower tract culture localization (2-glass test)
- Optional (selected cases)
  - Cytology
  - Imaging
  - Cystoscopy
  - Urodynamics

TABLE 2

Evaluation of a Patient (Male or Female) With Interstitial Cystitis/Bladder Pain Syndrome

- History (including voiding diary)
- Validated symptom score (eg, O'Leary-Sant)
- Physical examination (specifically a digital rectal and/or pelvic examination)
- Urinalysis, culture
- Optional
  - Cytology
  - Ultrasound
  - Cystoscopy (with or without hydrodistension under general anesthetic)

TABLE 3

Traditional Medical Therapies for Chronic Prostatis/Chronic Pelvic Pain Syndrome

- Antibiotics
- α-blockers
- Anti-inflammatories
- Phytotherapies (herbals)
- Neuromodulatory therapies (tricyclic antidepressants/gabapentinoids)
- Muscle relaxants and anxiolytics
- Selected patients
  - 5-α reductase inhibitors
  - Pentosanpolysulfate sodium

TABLE 4

UPOINT

- U for Urinary
- P for Psychosocial
- O for Organ specific (prostate and/or bladder)
- I for Infection
- N for Neurogenic (or systemic)
- T for Tenderness of skeletal muscle

significant improvement in over 80% of patients.

Dr. Robert Evans (Wake Forest University, Winston-Salem, NC) presented the list and evidence for the bladder-based therapy of UCPPS (IC/BPS) using the grading of recommendations from the recent AUA guidelines. These are listed in Table 5.

Dr. Evans broke down bladder-specific therapy into those directed toward mechanistic categories (Table 6). Intravesical therapies include variations of DMSO, heparin, lidocaine, and sodium bicarbonate. He discussed the impact of hydrodistension, which can be short lived. Combining that with fulguration of Hunner's lesions can result in significant, but again temporary, amelioration of symptoms.

Dr. Christopher K. Payne (Stanford University, Stanford, CA) urged the audience to consider pelvic floor physical therapy for men and women with UCPPS. He demonstrated that pelvic floor dysfunction is very prevalent in patients with chronic pelvic pain and that focused pelvic floor physiotherapy has been shown to be effective in case series as well as sham-controlled studies. The physical examination of the pelvis is key to the diagnosis and subsequent successful therapy; urologists should make an effort to determine pelvic floor tone, pain, and painful trigger points. They should find a local physiotherapist who has been trained in this specialized type of physiotherapy. Dr. Payne stressed that physiotherapy can and should be used with other therapies directed toward other phenotypes associated with UCPPS. Follow-up and reassessment is important, not only for patients referred to physiotherapy, but for all patients diagnosed and treated by urologists for this condition.

TABLE 5

Evidence for Bladder-based Therapy of Urologic Chronic Pelvic Pain Syndrome

- Diet and stress management
- Medical therapy
  - Pentosan polysulfate sodium
  - Hydroxyzine
  - Amitriptyline
  - Cimetidine
- Bladder instillations
- Cystoscopy and hydrodistension
  - Fulguration/injection of Hunner's ulcers
- Neuromodulation
- Botox injection
- Cyclosporine
- Surgery

TABLE 6

Mechanistic Categories of Bladder-specific Therapy

- Glycosaminoglycan replacement
  - Pentosan polysulfate sodium
  - Over-the-counter CystoProtek or Cysta-Q
- Mast cell stabilization
  - Hydroxyzine hydrochloride/pamoate
  - Over-the-counter alternatives: diphenhydramine, cetirizine
  - Montelukast
- Neurogenic upregulation treatment
  - Amitriptyline or other tricyclic antidepressants
  - Gabapentin, pregabalin, topiramate
  - Milnacipran, duloxetine
- "End-stage interstitial cystitis"
  - Cyclosporine A (best for patients with Hunner's ulcers)

CystoProtek is manufactured by Meda Consumer Healthcare, Marietta, GA. Cysta-Q is manufactured by Farr Labs, Los Angeles, CA.

Dr. Claire Yang, MD (University of Washington, Seattle, WA), described neuromodulation therapy—the electrical stimulation of a nerve, spinal cord, or brain in order to change the nerve activity. Dr. Yang stressed that neuromodulatory therapy for CPPS is not a standard treatment and should only be considered after other traditional treatments have failed. With neuromodulation, signals are introduced through the nerves to either overcome the pain signals or divert them. They somehow alter the way that the brain is processing the pain signals so that it doesn't perceive them as pain or it doesn't perceive them as strongly. The literature on the use of neuromodulation suggests that it might play a role in the amelioration of UCPPS symptoms (particularly urinary symptoms for which it has an indication) in patients who have not responded to more traditional approaches of therapy.

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In a case-based panel discussion moderated by Dr. Nickel, the panelists expanded on how to differentiate between the various phenotypes in clinical practice, and how to strategically use the therapies described. This panel discussion is available on the AUA 2012 Annual Meeting Web site.[1] The panel concluded that, in 2012, these new approaches to therapy for UCPPS will lead to more successful patient outcomes.

[J. Curtis Nickel MD, FRCSC]

Prostate Cancer

There were many exciting presentations in the field of localized prostate cancer presented at this year's annual meeting of the AUA. Several podium presentations and posters caught my attention and deserve review.

The poster by Msangi and colleagues[2] from Michigan evaluated the anonymous online-reported practice of a large group of urologists related to prevention of prostate biopsy sepsis. They used an email/online survey to over 4000 practicing urologists, of whom nearly 450 responded (an approximate 10% response rate). Approximately 42% performed 5 to 10 prostate biopsies each month and 28% performed 10 to 15 each month. They showed that 72% had obtained preprocedural urine cultures, over 90% performed ≥ 10 core biopsies, 78% used fluroquinolones, over 50% start antibiotics the day before biopsy, and the majority continue with antibiotics after for > 1 day. Interestingly, 77% of those responding had a least one patient hospitalized for biopsy sepsis within the past year. Any death from prostate biopsy complications averaged 1.6% among the respondents. These alarming results demonstrate that many urologists do not follow AUA guidelines and that the complication rates (hospitalizations and death rate) are higher than previously reported by others.

Another poster by Dangle and colleagues[3] from Chicago compared the use of prostate cancer antigen 3 (PCA3) (a urine test for prostate cancer early detection) as a marker for progression among a cohort of men participating in active surveillance (AS) for very low-risk prostate cancer. Within their AS protocol, the men enrolled were aged > 60 years, stage T1c/T2a, Gleason score < 6, < 3 cores with cancer, no core ≥ 50% involved with cancer, and tumor volume < 5% of biopsy volume. They followed 113 men and showed marked variation in both the enrollment PSA and PCA3 levels and those values later taken at 6 and 12 months of AS. PSA decreased by an average of 0.71 ng/mL and 0.44 ng/mL at 3 and 6 months, respectively, whereas PCA3 levels increased by an average of 8.17 and 12.81 at 6 and 12 months, respectively. This marked intra-individual variability led the authors to suggest that PCA3 (like PSA) is an unreliable marker of disease "stability" or "progression" among men being followed for AS and at present cannot substitute for regular prostate biopsy.

Mullins and associates,[4] from Baltimore, investigated the impact of surgeon volume and surgical approach (open radical prostatectomy [RP] or laparoscopic robotic [RALP]) on postprostatectomy morbidity in Maryland hospitals from 2008 to 2011. The authors queried the Maryland Health Service Cost Review Commission database using discharge ICD-9 codes for cancer prostatectomy. Demographics, postoperative outcomes, length of stay (LOS), hospital readmissions (30 day), and need for intensive care unit (ICU) admission were evaluated. During this timeframe in Maryland, 4064 men underwent either RP or RALP. About 77% of the cases were handled by high-volume surgeons. When surgery was performed by a low-volume surgeon, the case was more likely to be robotic, and the patients were more likely to be of non-white ethnicity, have a longer LOS, and be more likely to be readmitted and/or need an ICU stay. The analysis likewise showed that high-volume surgeons had patients with a lower LOS, readmissions, and need for ICU. Once again, surgical

experience is demonstrated to markedly affect outcomes for prostate surgery.

Wong and colleagues,[5] from Melbourne, presented an excellent paper outlining an international multicenter study examining the various criteria used to select men for AS among men who elected to undergo RP. This group compared the "Klotz criteria" and the "Van den Berg Prostate Cancer Research International Active Surveillance (PRIAS) criteria" among a group of 800 men treated with RP from three centers in the United Kingdom, Canada, and Australia. They were specifically looking for upstaging (≥ 7 Gleason score) and upstaging (≥ pT3 disease). All 800 met the Klotz criteria and 410 met the PRIAS criteria as well. Klotz and PRIAS upgrading and upstaging was 51%, 43%, and 18%, 12%, respectively. They also reported that the predictors within criteria boundaries of finding high-risk disease at surgery were age, palpable disease, and more positive cores. The most interesting finding of this paper was that more men from Australia were reclassified (upstage or upgrade), 43% to 51%, when compared with Europe and North American sites, 23% to 25%, owing to, per the authors, more stringent selection criteria, thus less reclassification. These and other data presented all point to the need for an internationally agreed-upon set of selection criteria for AS.

Kim and associates,[6] from New York, presented a paper analyzing the trends in use of incontinence procedures after RP. Among the procedures studied were bulking agents, urethral slings, and artificial urinary sphincters (AUS). This group used the Surveillance Epidemiology and End Results cancer registry linked to Medicare claims data to identify men > age 65 years who underwent open or minimally invasive (MIS) prostatectomy between 2000 and 2007. Overall, data from 16,348 men were included (3523 were MIS). Approximately 6% of the men received a procedure (no difference between open and MIS). Risk increased with age, location (South), race (white), and comorbid state. Risk was lower for nonmetropolitan residence. Fifteen percent had more than one procedure; 39%, 13%, and 34% received bulking agents, slings, and AUS, respectively. The median time from prostatectomy varied with year of surgery, between 16 and 29 months. It is quite interesting that, in many studies, incontinence is reported at levels between 15% and 70%, yet only 6% of men seem to be receiving treatment for this. Could this represent under-use, under-reporting, or lack of physician information transfer to the patients?

Kim and associates, from New York, presented a paper analyzing the trends in use of incontinence procedures after RP. Among the procedures studied were bulking agents, urethral slings, and artificial urinary sphincters.

Finally, Sundi and colleagues,[7] from Baltimore, looked at outcomes for extraperitoneal MIS approach to RP among very obese patients. Between 2001 and 2011, 1023 men underwent an MIS prostatectomy by a single surgeon. Body mass index (BMI) distributed as < 25 in 563 patients, 25 to 30 in 152 patients, 30 to 35 in 25 patients, 35 to 40 in 28 patients, and > 40 in 13 patients. No differences in estimated blood loss, pathological stage, capsular incision, and surgical margin rate or perioperative complications were noted across the BMI categories. Thus, the authors suggested that, even among the extremely obese men (BMI > 40), MIS extraperitoneal surgery can be performed safely with no comparably favorable outcomes.

[Alan W. Partin, MD, PhD]

Autologous Muscle-Derived Cells for Treatment of Stress Urinary Incontinence

Findings from a multicenter trial may give urologists and urogynecologists another MIS treatment option for women with stress urinary incontinence (SUI). The late-breaking podium abstract showed that treating a woman with her own muscle-derived stem cells was both safe and effective. Unlike surgical treatments, this procedure takes place in a physician's office.

This prospective, phase II, multicenter, dose escalation study assessed the 12-month safety and potential effectiveness of four different doses of Cook MyoSite (Pittsburgh, PA) Autologous Muscle Derived Cells for treatment of SUI in women.[8]

Findings from a multicenter trial may give urologists and urogynecologists another minimally invasive treatment option for women with stress urinary incontinence (SUI). The late-breaking podium abstract showed that treating a woman with her own muscle-derived stem cells was both safe and effective.

This study enrolled 64 women (age 54 ± 1 year) who failed other treatments previously for SUI and who had no improvement in symptoms over the past 6 months. Patients received intrasphincter injection of either 10×10^6 (n = 16), 50×10^6

(n = 16), 100 × 10^6 (n = 24), or 200 × 10^6 (n = 8) autologous muscle-derived cells (AMDC), which were derived from biopsies of the quadriceps femoris. The primary outcome measure was safety determined by the incidence and severity of adverse events (AEs). Potential effectiveness of AMDC was assessed via 3-day incontinence diaries, 24-hour pad weights, and quality-of-life scores (eg, Urinary Distress Inventory [UDI-6], Incontinence Impact Questionnaire [IIQ-7]) at baseline and after 12 months of treatment.

The study was carried out at the Oakland University William Beaumont School of Medicine in Royal Oak, Michigan; Vanderbilt University Medical Center in Nashville, Tennessee; and Sunnybrook Health Sciences Centre in Toronto, Canada. The study was presented by Dr. Kenneth Peters from Beaumont and was funded by Cook MyoSite Inc., a Cook Group company.

In the physician's office, patients were administered local anesthesia and cells were collected through a needle biopsy of the patient's thigh muscle, which was then sent to Cook MyoSite, where AMDCs were isolated from the muscle. After 6 to 8 weeks, the AMDCs were available for treatment. The cells were injected into the sphincter as an office procedure under local anesthesia. Four different doses were studied over 12 months: 10 million cells, 50 million cells, 100 million cells, and 200 million cells.

Fifty-nine patients completed 12 months of follow-up, 1 patient was lost to follow-up, and 4 patients withdrew from the study. No serious treatment-related AEs were reported. Minor events related to biopsy included hematoma (2/64) and bleeding requiring sutures (1/64). Genitourinary events within 30 days of AMDC injection were limited to dysuria (3/64), pelvic/abdominal pain or cramping (3/64), vaginal and/or urethral itching (3/64), transient hematuria (2/64), increased frequency/urgency (1/64), and transient sensation of a foreign object in the urethra (1/64).

Patients with moderate to severe SUI (ie, ≥ 3 stress leaks over 3 days and ≥ 3 g increase in pad weight at baseline) were included in the effectiveness analysis. The percentage of patients who experienced ≥ 50% reduction in baseline stress leaks and pad weight increased with increasing dose is shown in Table 7. Out of the four different dose groups, 200 × 10^6 dose group at 12 months showed that 100% (6/6) of patients had ≥ 50% reduction in stress leaks and 83% (5/6) had ≥ 50% reduction in pad weight. Additionally, the 200 × 10^6 group had the highest percentage of patients with 0 to 1 leaks (83%, 5/6), Stamey scores of 0 (50%, 3/6), and ≥ 50% improvement in quality of life scores (83%, 5/6 for IIQ-7; 67%, 4/6 for UDI-6). The study's conclusions were that intrasphincter injection of AMDC at doses of 10, 50, 100, and 200 × 10^6 cells is safe. AMDC treatment may improve symptoms and quality of life in women with SUI and more patients may be responsive to higher doses of AMDC. A

Prostate cancer screening was a major focus at the 2012 AUA meeting. At the plenary session, updated results from the European Randomized Study of Screening for Prostate Cancer were presented. This is the largest randomized study of prostate-specific antigen screening and, at 11-year follow-up, they found that it reduced metastatic disease and led to a 21% reduction in prostate cancer-specific mortality.

TABLE 7

Percentage of Patients Meeting Each Endpoint at 12 Months[a]

	10 × 10^6	50 × 10^6	100 × 10^6	200 × 10^6
≥ 50% reduction in stress leaks	54% (7/13)	60% (6/10)	83% (15/18)	100% (6/6)
No stress leaks over 3 days	23% (3/13)	20% (2/10)	22% (4/18)	50% (3/6)
0–1 stress leaks over 3 days	31% (4/13)	40% (4/10)	44% (8/18)	83% (5/6)
≥ 50% reduction in pad weight	15% (2/13)	40% (4/10)	61% (11/18)	83% (5/6)
Stamey score of 0	8% (1/13)	20% (2/10)	6% (1/18)	50% (3/6)
≥ 50% improvement in IIQ-7	54% (7/13)	55% (6/11)	61% (11/18)	83% (5/6)
≥ 50% improvement in UDI-6	31% (4/13)	45% (5/11)	44% (8/18)	67% (4/6)

[a]Only patients with ≥ 3 stress leaks over 3 days and ≥ 3 g increase in 24-hour pad weight at baseline were included in this analysis. One patient in the 50 × 10^6 dose group did not complete her diary and pad test at 12 months. Reduction/improvement is calculated from baseline values.
IIQ-7, Incontinence Impact Questionnaire; UDI-6, Urinary Distress Inventory.

double-blind, randomized, placebo-controlled, confirmatory study of AMDC treatment for female SUI is currently underway (ClinicalTrials.gov Identifier: NCT01382602).[9]

[Jayabalan Nirmal, PhD, Michael B. Chancellor, MD]

Prostate Cancer Screening

Prostate cancer screening was a major focus at the 2012 AUA Annual Meeting. At the plenary session, updated results from the European Randomized Study of Screening for Prostate Cancer (ERSPC) were presented. This is the largest randomized study of prostate-specific antigen (PSA) screening and, at 11-year follow-up, they found that it reduced metastatic disease and led to a 21% reduction in prostate cancer-specific mortality.[10]

That notwithstanding, the United States Preventive Services Task Force (USPSTF) issued a Grade D recommendation against PSA screening on May 21, 2012.[11] The AUA issued a response stating that "the USPSTF, in disparaging the PSA test before a newer diagnostic is more readily available, does a great disservice to American men and may cause more harm than good. It is inappropriate and irresponsible to issue a blanket statement against PSA testing, particularly for at-risk populations such as black men and those with a family history of the disease. The USPSTF, in its recommendations, has overstated the harms and underestimated the benefits of prostate cancer testing."[12]

Indeed, numerous abstracts highlighted how numerous factors modify the risk of prostate cancer, and should be considered in screening decisions. For example, Muller and colleagues[13] demonstrated that men with a positive family history had a 1.79-fold increased risk of prostate cancer on biopsy after multivariable adjustment. Albright and associates[14] showed that family history data can be further refined, because the risk of prostate cancer differs based on the number of affected relatives and age of onset. Although these studies clearly show that not all men have the same risk of prostate cancer, the USPSTF recommendations extend to these high-risk groups despite unclear generalizability.

If the PSA test is rejected for screening of asymptomatic men, and is only ordered for men with symptoms, this may lead to a resurgence of advanced prostate cancer. For example, Kojima and colleagues showed that, in a Japanese population, men presenting with lower urinary tract symptoms were significantly more likely to have metastatic disease (18%) compared with men undergoing PSA screening (3%).[15] In the United States, in the future, if PSA testing is only ordered for men with symptoms, we would similarly expect an increase in the proportion of men presenting with advanced disease.

Another problem with the current USPSTF recommendation is that screening protocols have significantly evolved since the randomized trials were designed in the early 1990s. As discussed at the PSA Town Hall, the AUA and other organizations have recently incorporated a baseline PSA measurement at age 40 for risk stratification.[16] Many studies in screening and clinical populations have confirmed that baseline PSA measurements at a young age predict the future risk of prostate cancer diagnosis, metastasis, and death.[17] At the AUA meeting, Zhu and colleagues[18] presented new data on baseline PSA measurements performed in a pilot study of the ERSPC from 1991 to 1993. At a median follow-up of 16 years, the baseline PSA value was associated with overall prostate cancer risk, as well as the likelihood of metastasis or disease-specific death.

Instead of a one-size-fits-all approach, the baseline PSA measurement can aid in designing an individualized screening protocol. As in the National Comprehensive Cancer Network Guidelines, men with higher baseline PSA levels can undergo more frequent screening compared with men with lower baseline PSA levels.[19] Stone and associates[20] showed that men with higher PSA levels presented more frequently for PSA testing, suggesting that such risk-adapted practices are already being employed.

Another way to individualize screening protocols is through the use of genetic markers. Many single nucleotide polymorphisms have been associated with prostate cancer susceptibility and some are also associated with PSA levels. In fact, prior studies have shown that the risk of prostate cancer at a given PSA level differs by genotype. Helfand and colleagues[21] expanded on these findings by calculating genetically adjusted PSA levels. In practical terms, this means increasing the biopsy threshold for high genetic PSA producers to reduce unnecessary prostate biopsies while decreasing the biopsy threshold for low genetic PSA producers to avoid delayed diagnosis. Other studies showed that genetic markers on chromosome 8q24 are also associated with prostate cancer tumor volume in men undergoing radical prostatectomy.[22] Recent advances have made this type of genetic testing an inexpensive possibility, suggesting a potential future role in more personalized screening.

Several abstracts at the meeting described ongoing work at

improving screening protocols, including PSA kinetics and other novel ways to use the PSA measurement. Abstract 2067 suggested dividing PSA velocity by prostate volume.[23] In 1027 prostate biopsies in Korea, they showed that PSA velocity per volume was significantly higher in men with prostate cancer detected than those with a negative biopsy result (0.06 vs 0.027; $P < .01$). El-Shafei and colleagues[24] looked at PSA slope in 449 patients undergoing biopsy and showed that it had improved performance characteristics for the discrimination of high-grade disease. Finally, Benecchi and colleagues[25] created a nomogram including PSA acceleration (along with the ratio of free to total PSA, digital rectal examination findings, and prostate volume), which performed well for the prediction of high-grade disease in the internal validation. Further study of these PSA dynamic measurements is warranted in external populations due to these combined findings of improved assessment for clinically significant disease.

Other studies looked at free PSA and isoforms in screening and early detection. For example, Sasaki and colleagues[26] showed the value of free PSA in a large Japanese screening study. Prostate biopsy was recommended for a PSA > 4 ng/mL or PSA from 2 to 4 ng/mL with a free PSA ≤ 12%. Compared with the reference group with a free PSA > 22.2%, men with a free PSA ratio of 17.5% to 22.2%, 13.3% to 17.4%, and < 13.3% had a 5.4-, 8.9-, and 22.9-fold increased risk of prostate cancer, respectively. Lughezzani and associates[27] instead looked at the combination of PSA, free PSA, and [–2] proPSA in a mathematical formula known as the Prostate Health Index (PHI). They showed that the inclusion of PHI in a multivariable nomogram led to a significant improvement in predictive accuracy for extended biopsy results.

In addition, numerous abstracts examined PCA3, which has recently been approved by the FDA as an aid in repeat biopsy decisions. Wei and colleagues[28] reported on a multi-institutional Early Detection Research Network validation trial of PCA3 for initial and repeat prostate biopsy. In 850 eligible men, they reported a positive predictive value of 80% on initial biopsy and a negative predictive value of 88% for repeat biopsy. In addition, incorporating PCA3 into the Prostate Cancer Prevention Trial risk calculator significantly improved the prediction of overall and high-grade prostate cancer. Another group from New York suggested instead using the ratio of testosterone to PCA3.[29] In a small group of men undergoing biopsy (n = 177), the testosterone to PCA3 ratio had a higher area under the curve (0.737) than PCA3 alone (0.719) for discriminating biopsy results. These combined findings suggest the need for further investigation into the incorporation of PCA3 in multivariable risk assessment tools.

Finally, an important problem with screening and AS is the risk of complications after prostate biopsy, which was addressed by several abstracts. Toi and colleagues[30] performed a prospective, randomized trial of the addition of apical anesthetic injection to the standard basal lidocaine injection. Although there was no difference in complication rates between the groups, it failed to reduce pain as measured by the Visual Analog Scale.

In the ERSPC Rotterdam, our group examined 10,474 prostate biopsies and found a 4% frequency of febrile complications.[31] Although hospitalizations increased over time, the overall frequency was only 0.8%. As just described, because prostate cancer screening was associated with a substantial reduction in metastatic prostate cancer and disease-specific death in this population,[10] we concluded that the low absolute risk of serious complications should not itself deter healthy men from undergoing a recommended prostate biopsy. Moreover, other abstracts looked at ways to improve the safety of biopsy. Santomauro and associates[32] from the University of California–San Diego performed rectal swab cultures prior to biopsy and reported no biopsy-related infections in 235 patients after the initiation of this protocol (compared with a 9% annual rate of prerectal cultures). This suggests that prostate biopsy complications may be reduced through more targeted prophylaxis, leading to further improvements in the risk-benefit ratio.

[Stacy Loeb, MD]

With an estimated 242,000 diagnoses and 28,000 deaths in 2012, prostate cancer is the most common malignancy diagnosed in the United States, and is the second leading cause of cancer death among men. Despite this, most prostate cancer has an indolent natural history and does not progress to a clinically meaningful stage even in the absence of treatment.

Predictors of Outcome in Prostate Cancer

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among men. Despite this, most prostate cancer has an indolent natural history and does not progress to a clinically meaningful stage even in the absence of treatment. Indeed, the Prostate Cancer Intervention Versus Observation Trial (PIVOT) has recently demonstrated that men randomized to RP or watchful waiting had indistinguishable all-cause mortality.[33] AS is considered by many to be the preferred approach for most men but it is vastly underutilized. Moreover, men with high-risk disease oftentimes fail single modality treatment and may benefit from the addition of adjuvant therapy.

Therapeutic decisions in men with prostate cancer are cloaked with uncertainty. Available data, PSA level, biopsy Gleason score, clinical stage, and extent of tumor involvement alone and in combination can provide risk stratification. However, even for those patients found to have very low-risk cancers, AS remains underutilized as a primary treatment strategy due to acknowledged rates of under-grading and understaging. The result is the current overtreatment of many thousands of men who would not have experienced any symptoms or loss of life had their cancers never been diagnosed. A significant proportion of these men likely experienced long-term adverse effects of surgery, radiation therapy, androgen ablation, and other treatments that ultimately were unnecessary, and the costs of these avoidable treatments are calculable in the billions of dollars.

A clear need therefore exists for novel biomarkers that can help generate improved predictions, and by extension, better-informed decision-making about timing and intensity of treatment. Many candidate biomarkers have been proposed for this purpose. However, the majority correlate closely with Gleason grade or other established characteristics, and therefore offer little independent information. Even among those that show particular promise in initial studies, fewer still prove valuable on rigorous external validation. For this reason, PSA, stage, and Gleason score remain the only prognostic factors assayed in routine clinical practice. Several presentations at this year's annual meeting have addressed this critical unmet need.

Certainly the ultimate measure of the success of prostate cancer therapy is a reduction in all-cause mortality (ACM). Isariyawongse and colleagues[34] examined ACM and prostate cancer–specific mortality (PCSM) in 10,429 men treated with RP external beam radiotherapy or brachytherapy between 1995 and 2005. Median follow-up was 5.5 years with 14.7% of survivors followed for $>$ 10 years. Twelve percent of men died with 1.7% of deaths due to PCSM. Age, treatment modality, PSA biopsy Gleason score, and comorbidity predicted ACM. PCSM was foretold by age, PSA biopsy Gleason score, and clinical T stage. A nomogram demonstrating good concordance was created and may be found in the abstract.

Does early biochemical recurrence after RP alter survival? This was the subject of a presentation by Ta and colleagues.[35] Men undergoing RP in Victoria, Australia, between 1995 and 2000 were studied by linking cancer and death registries. Biochemical recurrence (BCR) was defined as two consecutive readings $>$ 0.2 ng/mL; 2116 men had BCR, 250 men died, and 3.8% of these men died from prostate cancer. The time to BCR strongly predicted death in men with adverse disease but did not correlate with PCSM in those with low-risk disease.

Punnen and colleagues[36] performed a multi-institutional analysis of the Cancer of the Prostate Risk Assessment–Post Surgical (CAPRA-S) score to predict outcome after RP. The University of California–San Francisco (UCSF) CAPRA-S is a novel predictor of outcome that has been gaining increasing use due, in part, to the transparency of its calculation (no black box). The authors used the Veterns Administration Shared Equal Access Regional Cancer Hospital database for their study. CAPRA-S assigns up to 3 points for preoperative PSA and RP Gleason score, up to 2 points for positive surgical margins and seminal vesicle invasion, and 1 point for extracapsular extention (ECE) and N+ status. A total of 2211 men were evaluated and one-third recurred. Five-year freedom from recurrence for low (CAPRA-S score 0-2), intermediate (CAPRA-S score 3-5), and high (CAPRA-S score 6-10) was 72%, 41%, and 14%, respectively. The concordance index measure of the overall test performance was better for the CAPRA-S score than for the Memorial Sloan Kettering (Stephenson) nomogram.

Controversy surrounds the impact of positive surgical margins (PSM), no doubt in part owing to different levels of pathologic interrogation of the surgical specimen. Oh and colleagues[37] evaluated this in 658 men with clinical T2 or T3a disease. Patients were cataloged as (1) 406 men with negative margins NSM and no ECE, (2) 99 with PSM and no ECE, (3) 63 with negative surgical margins (NSM) and ECE, and (4) 90 with PSM and ECE. In multivariate analysis, pathologic Gleason score, ECE, and prostate volume were independent predictors of PSM with a median follow-up of 36 months. A total of 76 patients had BCR. BCR-free survival was significantly better in

group 1 but there was no difference among groups 2, 3, and 4. PSM was significantly associated with freedom from BCR in groups 1 and 2 combined, but in groups 3 and 4, only Gleason score predicted BCR.

Iremashvili and associates[38] studied the number of positive cores in diagnostic and repeat biopsies in patients managed by AS. A total of 161 patients had at least two surveillance biopsies. Progression was defined as the presence of Gleason grade 4 to 5 cancer more than two positive cores or more then 20% involvement of any core with cancer. Median follow-up was 3.6 years and 28.6 % of patients progressed. Both the number of positive cores and percentage involvement were associated with progression risk in univariate analysis. Only the number of positive cores was significant in the multivariate analysis. The best model for progression was achieved by combining the number of cores positive in the diagnostic and first surveillance biopsy.

Selecting men for AS is difficult. daSilva and colleagues[39] studied the outcomes in men who would have qualified for AS and other low-risk men but elected radical prostatectomy. A total of 2617 of 9915 were selected as being qualified from their surgical series. They were considered to the AS qualified group if they had clinical stage T1 or T2 Gleason < 7, PSA < 10, 1 or 2 positive cores, and PSA density < 0.2. The LR group used the above parameters without PSA density and number of cores as selection requirements. The AS group had a significantly lower rate of extra prostatic extension and positive surgical margins. No difference between LR and AS groups was observed for BCR. The authors concluded that PSA density and number of cores positive are important factors in AS selection.

Three papers addressed the significance of positive lymph nodes. Froehehner and associates[40] studied prostate cancer patients with positive lymph nodes to assess survival. A total of 193 men were evaluated with a median follow-up of 7.3 years. Immediate hormone therapy was given to 94%. Independent prognostic factors included age > 70 years, Gleason score 8 to 10, and ≥ 3 positive nodes. Comorbidity was associated with mortality in the univariate but not multivariate models. PSA had no prognostic significance. Intriguingly, about one-third of patients without additional adverse prognostic features had survival similar to node negative men.

In another study of men with positive lymph nodes, Pierorazio and colleagues[41] reported the 30-year experience from Johns Hopkins. A total of 505 N+ men (2.5% of patients treated with RP between 1982 and 2011) were identified. Median total and positive nodes were 13.2 and 1.7, respectively. Of 135 men with a dominant unilateral nodule, positive nodes were ipsilateral in 59.3%, contralateral in 20.7%, and bilateral in 11.1%. Fifteen-year BCR-free, metastases-free, and cancer-specific survival were 7.1%, 41.5%, and 57.5%, respectively. Predictors of BCR, metastases, and cancer death in multivariate analysis included Gleason sum and percent positive lymph node (LN). Of note, the extent of LN dissection did not correlate with outcome.

Finally Abdollah and colleagues[42] studied 4938 men undergoing radical prostatectomy between 1993 and 2010. Patients were divided into four cohorts based on seminal vesicle invasion (SVI) and nodal status. Approximately 83.7% had negative SVI; 13.8% of men were N+ with a mean of 16.1 nodes removed. N+ was observed in 5.9% vs 53.8% of men with negative and positive SVI, respectively. At a mean follow-up of 62 months, there was a significant difference in cancer-specific survival in men with versus without N+ in the −SVI. However, in men with +SVI, N− patients and N+ had similar survival.

The *TMPRSS2-ERG* fusion has been the subject of numerous investigations. Gonzales-Roibon[43] described the Johns Hopkins experience in a nested case-control trial. They had previously shown that *ERG* alone expression is a surrogate for the fusion. They examined 444 men who had RP with recurrence and matched them to 444 controls on the basis of age, Gleason score, and pathological stage. ERG protein was assessed immunohistochemically. After multivariate analysis, 48.5% of recurrent cases had *ERG* expression—nearly identical to the control subjects (48.3%). The extent of staining also had no prognostic impact.

Cooperberg and colleagues[44] provided validation of a cell-cycle progression (CCP) gene panel to improve risk stratification in a modern RP cohort. They evaluated a 46 gene panel including 31 cell-cycle progression genes and 15 housekeepers to provide a CCP score (Prolaris™; Myriad Genetics Laboratories, Salt Lake City, UT). RNA was extracted from the paraffin-embedded formalin-fixed radical prostatectomy specimen. The CAPRA-S score was used, as was discussed earlier.[36] Patients operated at UCSF after 1994 with a minimum of 5-year follow-up were evaluated. BCR was defined as 2 PSA determinations > 0.2 ng/mL or any secondary treatment 6 months after surgery. A total of 413 men were studied and 82 recurred. The hazard ratio for each unit increase in CCP was 2.1 and this remained significant in multivariate analysis. The CCP was particularly useful for stratifying risk in men with

low-risk parameters (CAPRA-S 0-2). A model combining CAPRA-S and CCP was significantly better than CAPRA-S alone.

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Kidney Stones: Demographics, Pathophysiology, and Treatment Options

There were several presentations at the 2012 AUA Annual Meeting that provided useful information and insights into kidney stone demographics, the pathophysiology of this process, and how best to treat those afflicted. These papers are subsequently reviewed.

Information from two independent groups using the same database demonstrated that the prevalence of kidney stones is increasing in the United States. Scales and associates[45] queried the 2007-2008 National Health and Nutrition Examination Survey (NHANES) and found that there was a 71% increase in the prevalence of stones as compared with the 1988-1994 survey. This was true for both genders and all racial and ethnic groups. Shoag and Eisner[46] reported that there was a 69.4% increase in the prevalence in men and a 50% increase for women. This was also demonstrated for all racial and ethnic groups and was seen in those with BMI $>$ or $<$ 30, and in those with or without hypertension or diabetes mellitus.

Kidney stone formation has been linked to a number of medical comorbidities including cardiac disease, diabetes mellitus, hypertension, obesity, and chronic kidney disease. Shoag and colleagues[47] performed a multivariate analysis using the NHANES III survey and found that kidney stone formation was associated with an increased risk for peripheral vascular disease as well as death from this problem.

Hypercalciuria is a risk factor for the development of calcium-containing kidney stones in children and adults and it has been linked to bone disease in adults. Bagrodia and associates[48] reported that children with kidney stones are significantly shorter than those who do not form stones. This might be linked to metabolic disturbances impacting skeletal health. An increasing number of adults are forming calcium phosphate stones, especially those with recurrence. Wood and colleagues[49] reported this trend in children and noted that brushite stones are now seen more commonly in recurrent stone formers. Interactions between dietary calcium and oxalate in the gut are thought to impact stone risk and could be influenced by the relative amounts of each substance in a meal. Lange and associates[50] performed a study in which healthy adults were administered a large amount of dietary oxalate and a normal amount of calcium. Meals were administered either with the amounts of dietary calcium and oxalate being balanced for breakfast, lunch, and dinner, or imbalanced. Urinary collections throughout the day demonstrated no significant differences in stone risk between these two regimens. This suggests that, as long as a normal amount of dietary calcium is consumed, the sequence in which this is done does not alter stone risk when increased amounts of dietary oxalate are eaten.

Urinary uric acid is thought to promote calcium oxalate stone formation and urinary magnesium is considered an inhibitor. Riley and colleagues[51] used molecular dynamic simulations using Not (just) Another Molecular Dynamics program and Chemistry at Harvard Macromolecular Mechanics force fields in an attempt to define how these chemicals may impact stone formation. They demonstrated that uric acid prolongs the contact time between calcium and oxalate, thus perhaps allowing for the perfect storm: stone formation while magnesium reduces this interaction.

Shock wave lithotripsy is still commonly used to treat patients with renal and ureteral stones. Modifications in technique have been demonstrated to enhance results including proper application of coupling gel. If this is not done correctly air pockets in the gel may alter focal zone acoustics that are involved in stone comminution. The Indianapolis group was the first to recognize this and reported at this meeting that it occurred most commonly when the air pockets were near the center of the coupling field.[52] Therefore, special attention is especially important when applying gel to this area.

Patients may have associated sepsis with stone events and require appropriate and timely antibiotic therapy. Marien and colleagues[53] reported that antibiotic resistance is now common in patients with obstructing ureteral stones, fever, and associated urinary tract infection. Therefore, it is important for the practitioner to be aware of local resistance patterns when selecting antibiotic regimens in this clinical scenario. The performance of stone cultures in patients undergoing percutaneous nephrostolithotomy (PCNL) is now being increasingly advocated. Information from two studies was presented at this meeting to justify this practice. De Cogain and associates[54] and Bhojani and colleagues[55] reported that 10% to 20% of patients with sterile urine will have positive stone cultures, including patients with metabolic

stones. The latter group reported discordance between urine and stone cultures. Therefore, a stone culture provides a head start on isolating and characterizing the pathogen causing sepsis during or after PCNL.

An increasing number of people are using iPad® technology (Apple, Cupertino, CA) and this may now facilitate PCNL. Rassweiler and associates[56] placed radiodense spherical markers on patients before PCNL who then underwent a thin-slice computed tomography (CT) in the prone position. Three-dimensional reconstructions are then performed to define the kidney, the stone material, their relationships with surrounding structures, and the markers. The iPad camera is used to locate the markers. This information is sent to a server where an analysis of the marker positions is combined with the CT information to create an augmented reality-enhanced image. The latter is forwarded back to the iPad and used to direct access into the safest targeted calyx without fluoroscopic or ultrasound imaging. After the calyx is entered, fluoroscopic imaging is used to monitor guidewire and access sheath manipulations.

Concerted efforts are now being undertaken to limit the amount of radiation exposure to patients during diagnostic and interventional procedures. Patients undergoing ureteroscopic and PCNL procedures are exposed to such ionizing radiation. The use of pulsed fluoroscopy may reduce this exposure. Elkoushy and colleagues[57] performed a retrospective study in which patients undergoing these procedures were subjected to pulsed or standard fluoroscopy and found that the pulsed mode was associated with significantly lower fluoroscopy time. A prospective study is needed comparing both techniques, including an assessment of image quality and its impact on performing the procedure.

The aforementioned profile clearly demonstrated the many advances in stone research and how to best care for this cohort. The reader is directed to read these abstracts and await the anticipated peer-reviewed publications generated.

[Dean Assimos, MD]

Pediatric Urology

Compared with the adult population with infertility, there is a paucity of literature with normative data on semen analyses in adolescents. Most infertility specialists recommend two separate specimens due to the degree of within-subject variability. The study cohort by Christman and colleagues[58] included 79 patients with a mean age of 18.8+ 1.2 years with a history of undescended testis or varicocele. Each patient submitted two separate semen specimens at around age 18 years. The total motile count (TMC) was defined as abnormal ($<$ 20 million/ejaculate) or normal ($>$ 20 million/ejaculate). The initial semen analysis had a TMC of 39.8 + 92.8 million and the second, 52.1 + 103.1 million. The mean within-subject difference in TMC was –12.3 + 52.1. There was a statistically significant correlation between the two semen specimens, with concordance between the samples in 86%. The κ statistic was 0.66, inferring a moderate-to-substantial agreement when the samples were stratified into low or normal TMC. The authors conclude that although there is a large degree of within-patient variability of individual semen analyses, there is moderate to substantial agreement between consecutive semen specimens in late adolescence when stratified by TMC. Therefore, it is likely that a single specimen is sufficient to classify these adolescents as they transition to adult care.[58]

Management of the adolescent varicocele remains unknown because it is common in the male population (15%) and may have no clinical effect on fertility. The investigators from Children's Hospital of Philadelphia hypothesized that adolescents with varicoceles will not have a high prevalence of suboptimal semen analyses when followed with active surveillance.[59] A cohort of 70 adolescents with a mean age of 15.6 years who had palpable varicoceles was followed using serial physical examinations and scrotal ultrasound to detect significant size discrepancies. Semen analysis was performed at about age 18 years. Indications for surgical intervention were pain, consecutive testicular volume differential $>$ 20% of ultrasound, and/or abnormal semen analyses (TMC $<$ 20 million motile sperm per ejaculate). Most patients were followed for about 3 years prior to submitting a semen analysis. Of the 67% with a low TMC, 60% underwent a second sample and almost all (93%) remained low when the samples were averaged. A mean of 3.5 scrotal ultrasounds were performed per patient. Varicocelectomy was performed in 19% (13/70). The authors concluded that active surveillance of the adolescent varicocele is associated with a high prevalence of suboptimal semen analyses. The adolescent varicocele appears to impact negatively on future spermatogenic potential and may warrant early, more aggressive treatment versus those varicoceles identified in the asymptomatic adult.[59]

[Ellen Shapiro, MD, FACS, FAAP]

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